

CLAIMS

We claim:

1. A process for preparing cilostazol comprising:
 - a) dissolving 6-hydroxy-3,4-dihydroquinolinone and a water-soluble base in water to form an aqueous phase,
 - b) dissolving a 1-cyclohexyl-5-(4-halobutyl)-tetrazole in a water-immiscible solvent to form an organic phase,
 - c) forming a biphasic mixture by contacting the aqueous phase and the organic phase in the presence of a quaternary ammonium phase transfer catalyst,
 - d) and recovering cilostazol from the biphasic mixture.
2. The process of claim 1 wherein the molar quantity of the 6-hydroxy-3,4-dihydroquinolinone is greater than the molar quantity of the 1-cyclohexyl-5-(4-halobutyl)-tetrazole.
3. The process of claim 1 wherein the water-immiscible solvent is selected from the group consisting of toluene, hexane, dichloromethane and mixtures thereof.
4. The process of claim 1 wherein the quaternary ammonium phase transfer catalyst is selected from the group consisting of tricaprylmethylammonium chloride, tetra-n-butylammonium bromide, benzyltriethylammonium chloride, cetyltrimethylammonium bromide, cetylpyridinium bromide, N-benzylquininium chloride, tetra-n-butylammonium chloride, tetra-n-butylammonium hydroxide, tetra-n-butylammonium iodide, tetra-ethylammonium chloride, benzyltributylammonium bromide, benzyltriethylammonium bromide, hexadecyltriethylammonium chloride, tetramethylammonium chloride, hexadecyltrimethyl ammonium chloride, and octyltrimethylammonium chloride.
5. The process of claim 4 wherein the quaternary ammonium phase transfer catalyst is selected from the group consisting of tricaprylmethyl ammonium chloride, tetrabutylammonium bromide, triethylbenzylammonium bromide and mixtures thereof.
6. The process of claim 5 wherein the quaternary ammonium phase transfer catalyst is tricaprylmethyl ammonium chloride.

7. The process of claim 1 wherein the water-soluble base is an alkali metal hydroxide, carbonate or bicarbonate.
8. The process of claim 7 wherein the water-soluble base is selected from the group consisting of NaOH, KOH, K₂CO₃, Na₂CO₃ and NaHCO₃.
9. The process of claim 7 wherein the water-soluble base is NaOH.
10. The process of claim 1 further comprising dissolving a reaction promoter selected from the group consisting of potassium carbonate and sodium sulfate in the water.
11. The process of claim 1 wherein the 1-cyclohexyl-5-(4-halobutyl)-tetrazole is 1-cyclohexyl-5-(4-chlorobutyl)-tetrazole.
12. A process for preparing cilostazol comprising:
 - a) adding 6-hydroxy-3,4-dihydroquinolinone, a 1-cyclohexyl-5-(4-halobutyl)-tetrazole, from about 0.9 to about 1.2 equivalents of an alkali metal hydroxide with respect to the dihydroquinolinone, and from about 0.1 to about 0.2 equivalents of an alkali metal carbonate with respect to the dihydroquinolinone to a non-aqueous hydroxylic solvent to form a reaction mixture, and
 - b) recovering cilostazol from the reaction mixture.
13. The process of claim 12 wherein the about 0.9 to about 1.2 equivalents of alkali metal hydroxide is added in one portion.
14. The process of claim 12 wherein the alkali metal hydroxide is added by adding a first portion of the alkali metal hydroxide and after addition of the 6-hydroxy-3,4-dihydroquinolinone, 1-cyclohexyl-5-(4-halobutyl)-tetrazole, and alkali metal carbonate, adding a second portion of the alkali metal hydroxide.
15. The process of claim 14 further comprising adding a third portion of the alkali metal hydroxide after the second portion.
16. The process of claim 12 wherein the non-aqueous hydroxylic solvent is selected from the group consisting of 1-butanol, isopropanol, 2-butanol and amyl alcohol.
17. The process of claim 16 wherein the non-aqueous hydroxylic solvent is 1-butanol.
18. The process of claim 12 wherein the alkali metal hydroxide is potassium hydroxide and the alkali metal carbonate is potassium carbonate.

19. The process of claim 12 wherein the molar quantity of the 6-hydroxy-3,4-dihydroquinolinone is greater than the molar quantity of the 1-cyclohexyl-5-(4-halobutyl)-tetrazole.
20. The process of claim 12 wherein the molar quantity of the 1-cyclohexyl-5-(4-halobutyl)-tetrazole is greater than the molar quantity of the 6-hydroxy-3,4-dihydroquinolinone.
21. The process of claim 12 further comprising removing water that is formed by combining the 6-hydroxy-3,4-dihydroquinolinone and alkali metal in the hydroxylic solvent with molecular sieves.
22. The process of claim 12 wherein the 1-cyclohexyl-5-(4-halobutyl)-tetrazole is 1-cyclohexyl-5-(4-chlorobutyl)-tetrazole.
23. A process for preparing cilostazol comprising dissolving 6-hydroxy-3,4-dihydroquinolinone in a non-aqueous solvent, activating the phenol group of 6-hydroxy-3,4-dihydroquinolinone with an alkali metal hydroxide to form 6-hydroxy-3,4-dihydroquinolinone phenolate, scavenging water formed as a byproduct of the phenol activation from the solvent by entrainment in molecular sieves, and thereafter adding a 1-cyclohexyl-5-(4-halobutyl)-tetrazole and recovering cilostazol from the solvent.
24. The process of claim 23 wherein the alkali metal hydroxide is sodium hydroxide or potassium hydroxide.
25. The process of claim 23 wherein the non-aqueous solvent is selected from the group consisting of 1-butanol, toluene, hexane, dichloromethane and mixtures thereof.
26. The process of claim 23 wherein the 1-cyclohexyl-5-(4-halobutyl)-tetrazole is 1-cyclohexyl-5-(4-chlorobutyl)-tetrazole.
27. A process for purifying cilostazol by recrystallization from a solvent selected from the group consisting of 1-butanol, acetone, toluene, methyl ethyl ketone, dichloromethane, ethyl acetate, methyl t-butyl ether, dimethyl acetamide-water mixtures, THF, methanol, isopropanol, benzyl alcohol, 2-pyrrolidone, acetonitrile, Cellosolve, monoglyme, isobutyl acetate, sec-butanol, tert-butanol, DMF, chloroform diethyl ether and mixtures thereof.

28. Highly pure cilostazol free of impurities.
29. Micronized cilostazol of small particle size and narrow particle size distribution.
30. Substantially pure cilostazol prepared by the process of any of claims 1, 12 and 23.